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The Evolution of Antihypertensive Therapy: An Overview of Four Decades of Experience

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Hypertension is a major public health problem amenable to treatment. Numerous large scale clinical trials have demonstrated that effective, sustained control of elevated arterial pressure to a level below 140/90 mm Hg results in reduced cardiovascular morbidity and mortality. Over the past 4 decades antihypertensive drug therapy has evolved from a stepwise, but physiologically rational, selection of agents to specific programs tailored to individualized therapy for specific clinical situations. This evolution has taken place because of a greater understanding of the pathophysiology of hypertensive diseases, the development of new classes of antihypertensive agents that attack specific pressor mechanisms, and the ability to wed these concepts into a rational and specific therapeutic program.

Thus, with the currently available spectrum of antihypertensive therapy, we are now able to select treatment for special patient populations utilizing a single agent and, therefore, we can protect the heart, brain and kidneys and maintain organ function without exacerbating associated diseases. These benefits are clear-cut and have resulted in many millions of patients becoming the beneficiaries of this transfer of careful, painstaking and purposeful investigative experiences into clinical practice.

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The introduction of indirect blood pressure measurement in the mid 19th century has permitted the later correlation with hypertensive diseases (1). Thus, over the past 150 years, a number of fundamental and clinical concepts have been elucidated, permitting a greater understanding of the pathophysiology of hypertensive diseases. These include a clearer understanding of pressor and depressor mechanisms that involve neurohumoral, hormonal, cardiovascular and renal responses that control arterial pressure (2–6). Hence, a better comprehension of these mechanisms has enabled the purposeful development and application of several different classes of therapeutic agents that intercede in the responses of these systems and ultimately correct the abnormally elevated arterial pressure.

Over these past 40 years, the emergence of numerous therapeutic innovations and drug discoveries has resulted in better control of hypertensive disease (Table 1). With greater understanding of these new classes of agents, it was possible to regulate arterial pressure and develop therapeutic regimens that have progressed from direct-acting smooth muscle relaxing vasodilators that require diuretics to protect against intravascular fluid expansion, to more specific agents that act on cardiovascular function through specific mechanisms that control vascular smooth muscle tone and cardiac responses [e.g., alpha- or beta-adrenoreceptor inhibition, calcium antagonism or angiotensin-converting enzyme inhibition].

The evolution of these major classes of antihypertensive agents, their mechanisms of action and hemodynamic effects, as well as their relations to specific cardiovascular risk factors are reviewed. Our discussion emphasizes their relation to specific cardiovascular problems that are associated with hypertension and suggests an evolved approach for tailoring antihypertensive therapy.

This article is part of a series of articles celebrating the 40th anniversary of the American College of Cardiology. The series attempts to set the stage for the future by describing current state of the art management of selected major cardiovascular problems and the basic knowledge that will provide directions for advances in diagnosis and therapy.

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Table 1. Evolutionary Use of Antihypertensive Drugs

Drugs or Drug Classes	Year*
Ganglionic blocking agents (hexamethonium, trimethaphan, tetraethylammonium chloride, pentolinium tartrate)	Late 1940s
Rauwolfia and veratrum alkaloids (reserpine, cryptenamine tannate)	1931 (India), 1952 (United States)
Vasodilator (hydralazine)	1951
Alpha-adrenergic receptor blockers (phentolamine, phenoxybenzamine)	1954
Thiazide diuretics (chlorothiazide, hydrochlorothiazide)	1957
Post-ganglionic blocker (guanethidine)	1959
Potassium-sparing diuretics (spironolactone, amiloride, triamterene)	1958 to 1964
Central alpha$_2$-receptor agonist (methyldopa, clonidine)	1963 and 1974
Beta-adrenergic receptor blockers (propranolol)	1964 (Europe), 1974 (United States)
Vasodilator (minoxidil)	1968
Peripheral alpha$_1$-adrenergic receptor blocker (prazosin)	1976
Calcium channel antagonist (verapamil)†	1980
Angiotensin-converting enzyme inhibitor (captopril)	1981
Alpha-beta-adrenergic receptor blocker (labetalol)	1984
New investigational classes of drugs:	1990s
Serotonergic receptor antagonists (ketanserin)	
Selective dopamine$_1$ antagonists (fenoldopam)	
Renin inhibitors	

*Year approved for use as antihypertensive agent in the United States unless otherwise noted. †Verapamil was synthesized and used for investigation as early as 1962 in Europe.

Agents That Inhibit the Sympathetic Nervous System

A number of neural mechanisms serve to modulate circulatory control of arterial pressure (6,7) including neural afferents in baroreceptors (or mechanoreceptors) located in arteries, veins and the heart (7). Signals from these receptors travel centrally to the medullary vasomotor centers of the brain and result in efferent reflexive cardiovascular responses. These efferent impulses are conducted to the periphery by means of sympathetic and parasympathetic nerve fibers to affect changes in vessel caliber, heart rate and myocardial contractility through the release of various neurohumoral substances (i.e., catecholamines, indoles and peptide hormones). The responses elicited by these impulses modulate cardiovascular and renal homeostatic regulation of arterial pressure (6–9).

Therapeutic agents that modify neural input to the cardiovascular and renal systems were among the first introduced for the management of hypertensive diseases (9). Over the years, this array of compounds has permitted the possibility of virtual pharmacologic dissection of the entire autonomic nervous system. Thus, it is possible to select agents that inhibit outflow of impulses from various cardiovascular control centers in the brain, ganglionic neurotransmission, release of neurohumoral substances from nerve endings, and alpha- or beta-adrenoreceptors, or both, on presynaptic nerve endings or at postsynaptic sites on cardiac and vascular smooth muscle cells (10,11).

Ganglionic Blockers

This potent group of antihypertensive agents (e.g., hexamethonium, trimethaphan) was synthesized in the late 1940s and was the first group used to treat hypertension (12,13). They inhibit the neurotransmission at the thoracolumbar ganglia by blocking the action of released acetylcholine to interfere with postganglionic neuronal propagation of the impulse (13). This results in reduced sympathetic tone as well as arterial and venodilation. The pressure fall is most pronounced with upright posture, as a result of peripheral blood pooling and reduced venous return to the heart (13). Declines in arterial pressure, therefore, result from a diminished cardiac output, as well as reduced total peripheral resistance (13,14). Although these agents are less used today, they were responsible for the dramatic reversal of morbidity from malignant hypertension and other severe hypertensive complications in the early years of therapy (15). However, trimethaphan continues to be used for the management of certain hypertensive crises (e.g., dissecting aortic aneurysm) and for intraoperative control of arterial pressure (15,16).

Postganglionic Adrenergic Inhibitors

Reserpine. This agent was introduced in the mid 1950s and is still widely used throughout the world. It acts by depleting neurotransmitters (e.g., norepinephrine, epinephrine, serotonin) from postganglionic nerve endings as well as

in the brain (11,17). As a result, arterial pressure and total peripheral resistance are reduced, heart rate slowed and cardiac output, as well as renal blood flow, maintained (18,19).

The Veterans Administration cooperative studies (20,21) supplied some of the first evidence that low doses of reserpine (0.1 to 0.5 mg/day), in combination with a diuretic, effectively lower arterial pressure with relatively few side effects. Shortly thereafter, these landmark Veterans Administration multicenter studies (22,23) demonstrated a dramatic reduction in cardiovascular morbidity and mortality as well as diminished progression of diseases associated with hypertension. Furthermore, studies (24–29) with a number of adrenergic inhibitors (e.g., the centrally acting agents and β-adrenoreceptor blockers) as well as angiotensin-converting enzyme inhibitors and calcium channel antagonists have shown reversal of left ventricular hypertrophy, a known risk factor for myocardial infarction. Reserpine is less used today in this country because of the availability of other agents with less troublesome side effects.

Guanethidine. This agent became available for management of hypertension in the late 1950s and remains one of the most potent sympatholytic drugs (30). It acts by depleting norepinephrine from the postganglionic nerve ending but, unlike reserpine, it has no central action (30–32). This results in a reduced total peripheral resistance and venous tone that permits a fall in arterial pressure, particularly with assumption of upright posture. When this drug is given intravenously, it produces a transient rise in arterial pressure secondary to catecholamine release (32,33). This increase in pressure may be attenuated by pretreatment with alpha-adrenergic receptor blocking drugs (11,32).

Prolonged therapy with guanethidine results in a negative cardiac chronotropic and inotropic effect secondary to myocardial catecholamine depletion (34). The reduced venous return results from peripheral venous pooling, accounting for the reduction in cardiac output and possible decrease in blood flow to major circulatory beds including the kidney (35). Furthermore, intravascular volume expansion attenuates its hypotensive effect, a problem that is resolved by the addition of a diuretic (36,37).

Guanethidine has been used less frequently in recent years, even if hypertension is severe, primarily because of the availability of other potent and specific agents with fewer side effects. However, a congener of guanethidine, guanadrel, is used for the treatment of mild to moderate hypertension in less potent dosages. Nevertheless, its mechanism of action is similar to that of guanethidine.

Peripheral Alpha-Adrenergic Inhibitors

The first alpha-adrenoreceptor blocking agents used for hypertension were phentolamine and phenoxybenzamine (38). These agents inhibit norepinephrine stimulation of both postsynaptic ($alpha_1$) and presynaptic ($alpha_2$) adrenergic receptor sites. The major clinical indications for phentolamine (an intravenous compound, or phenoxybenzamine (for oral use) are hypertensive states associated with catecholamine excess (e.g., pheochromocytoma, clonidine withdrawal) (38,39). These agents, like the foregoing adrenolytic agents, also re-expand intravascular (plasma) volume associated with pressure reduction. This action has been exploited clinically in the preoperative preparation of patients with pheochromocytoma. These agents prevent intraoperative hypotension associated with tumor removal in these patients with catecholamine-induced volume contraction (39). These agents do not prevent cardiac arrhythmias associated with catecholamine excess, a problem that may be alleviated with beta-adrenoreceptor blockers (40).

The more selective $alpha_1$-receptor antagonists directly inhibit norepinephrine stimulation of these receptor sites on vascular smooth muscle without altering myocardial contractility, cardiac output or reflexively stimulating an increase in heart rate (41). This lack of reflex increase in heart rate, even with rapid pressure reduction following the first dose, has been attributed to direct $alpha_1$-receptor inhibition at the cardiac myocyte (41–43). The clinical manifestations of the "first does phenomenon" (e.g., orthostatic hypotension) may be minimized by initial administration of prazosin at bedtime.

The $alpha_1$ adrenoreceptor inhibitors now include a number of agents (i.e., prazosin, terazosin, doxazosin and indoramin), each of which dilates the arterioles, thus reducing arterial pressure (41,42). In addition to arterial pressure reduction, these agents have been used to treat patients with congestive heart failure. By virtue of their potential vasodilating effect on constricted peripheral venules, $alpha_1$-adrenoreceptor blockers reduce cardiac preload as well as afterload, an effect not observed in patients with uncomplicated hypertension (44). However, this beneficial effect on systemic hemodynamics, noted in early studies with prazosin, was not substantiated. Furthermore, long-term studies in patients with heart failure demonstrated a tachyphylactic response with prolonged use of the drug (44). This response presumably is secondary to maximal $alpha_1$-adrenoreceptor blockade. Thus, the use of prazosin in patients with heart failure has diminished, although this may reflect the more recent introduction of the angiotensin-converting enzyme inhibitors.

Centrally Active $Alpha_2$-Receptor Agonists

Clonidine. This drug, an imidazoline derivative, is a prototype of agents that stimulate central $alpha_2$-receptors (45,46). It is related chemically to tolazoline and phentolamine, although it has few direct peripheral vasodilating effects in therapeutic dosages (46). Clonidine acts by stimulating $alpha_2$-receptors in the nucleus tractus solitarii of the

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brain which, in turn, decrease central adrenergic outflow to the heart, vessels and kidney (47). Thus, the resultant fall in arterial pressure is not accompanied by reflex tachycardia (46,48). Interestingly, the hypotensive effect of central alpha$_2$ receptor agonists is attenuated in the presence of tricyclic antidepressant medications, a response that is apparently independent of the alpha$_2$-receptor (49).

With long-term treatment, clonidine decreases total peripheral resistance in both supine and standing positions. Furthermore, cardiac output and oxygen consumption, in response to exercise, remain unchanged from pretreatment values (49). In addition, clonidine does not alter renal blood flow, glomerular filtration rate or renal sodium handling; however, renin release is suppressed (50).

Clonidine acts promptly and, when administered at hourly intervals, may be useful in treating hypertensive urgencies and emergencies (15). If clonidine is withdrawn abruptly, rebound hypertension may ensue, possibly leading to a hypertensive crisis (51). However, the newer and longer-acting agents (e.g., guanabenz, guanfacine) may not be associated with this adverse effect (52). Other side effects produced by clonidine and shared by all central alpha$_2$-receptor agonists include drowsiness, dry mouth and impaired sexual function (19,46). These problems may limit their clinical usefulness.

Methyldopa. This agent is the other prototype of a centrally active alpha$_2$-receptor agonist. It was synthesized in the early 1950s and described as a dopa-decarboxylase inhibitor (53). Later, false neurohumoral transmission (54) and other antihypertensive mechanisms including direct inhibition of central vasomotor centers (55) and renal suppression of renin release (56) were suggested. At present it appears to act similarly to clonidine, although it must be initially metabolized in the nuclei tractus solitarii neurons to alpha-methyl-norepinephrine, the direct central alpha$_2$-receptor agonist (57).

Hemodynamically, methyldopa acts promptly (within a few hours) to reduce arterial pressure through a slight decrease in cardiac output that is associated with a diminished total peripheral resistance (58,59). This decline in output is transient and does not affect renal blood flow or glomerular filtration rate. Thus, renal function is preserved even in patients with renal insufficiency (10,60). In addition to the side effects described for clonidine, hepatocellular dysfunction and a Coombs' test positive for hemolytic anemia have been reported with methyldopa administration (10,11,19).

Beta-Adrenergic Receptor Antagonists

Pronethalol was the first beta-adrenoreceptor blocker synthesized (61), but it was not used clinically because of adverse effects. Shortly thereafter, propranolol, a beta$_1$- and beta$_2$-adrenoreceptor blocker, was introduced for the treatment of angina pectoris and hypertension (62). Since then, many other compounds have been introduced, including agents that are more water-soluble (nadolol, atenolol) (63,64); agents with intrinsic sympathomimetic activity (oxyprenolol, pindolol, acebutolol) (65,66); and those with some degree of cardioselectivity (atenolol, metoprolol, acebutolol) (64,66–68). Notwithstanding these varied characteristics, in the dosages employed for the treatment of hypertension and angina pectoris, their more receptor-specific actions appear to have little variance. Despite their widespread use over the past 25 years, their antihypertensive action remains unresolved. However, a number of mechanisms have been postulated, including a decreased cardiac output (69), resetting of arterial baroreceptors (70), reduction in circulating plasma renin activity (71), central adrenoreceptor stimulation (19,72) and peripheral alteration of catecholamine release (73).

Hemodynamically, the beta-adrenoreceptor inhibitors decrease heart rate, cardiac output and myocardial oxygen consumption and increase total peripheral resistance (66,69). Conversely, renal blood flow and glomerular filtration rate are maintained despite reductions in cardiac output in the supine position (66). However, studies (74) examining the renal effects of propranolol demonstrate that quiet standing significantly decreases renal blood flow and results in avid sodium retention in normal and hypertensive subjects. Whereas these agents are useful in patients with uncomplicated essential hypertension and ischemic heart disease, their cardiac and renal hemodynamic effects and other metabolic effects may preclude their use in patients with other conditions (e.g., diabetes mellitus, congestive heart failure, pulmonary disease, peripheral arterial insufficiency).

These agents may also have adverse effects on lipid profiles (75,76), and some studies have shown that nonspecific beta-blockers increase triglycerides and decrease the ratio of high density lipoprotein (HDL) to low density lipoprotein (LDL) cholesterol. No such adverse effects on HDL/LDL cholesterol ratios have been shown with agents having intrinsic sympathomimetic activity (76). Nevertheless, a number of large scale, double-blind, prospective trials (77–84) with beta-adrenoreceptor blockers clearly demonstrate both a reduction in cardiovascular morbidity and mortality and improved myocardial preservation. Thus, these agents serve to protect patients with prior myocardial infarction from increased myocardial oxygen demands and high circulating catecholamines, factors that contribute to cardiac arrhythmias in this setting. Furthermore, these agents diminish the mass of the hypertrophied left ventricle (85) and lessen symptoms from angina pectoris (86).

Several studies have compared the effects of the thiazide diuretics with the beta-blockers (most notably, propranolol) (77,80,82,84). Trials conducted by the Medical Research Council and the Australian Mild Hypertension Group (77,79) demonstrated that the thiazide diuretics protected hyperten-

sive patients who were smokers from subsequent stroke better than propranolol, even though the two agents were equally efficacious in controlling arterial pressure. At present, there is no available explanation for this finding.

Combined Alpha- and Beta-Blocker

Labetalol combines (within the same molecule) nonselective beta-adrenoreceptor, as well as alpha$_1$-receptor inhibitory properties. This agent lowers arterial pressure by reducing total peripheral resistance without changing resting heart rate or cardiac output (87,88). Thus, when administered intravenously, arterial pressure falls promptly without the reflex stimulation of the heart (88). Hence, this agent is useful in patients with hypertension and other concomitant problems (i.e., symptomatic coronary artery disease, congestive heart failure or hypertensive emergencies with and without dissecting aneurysm) (89).

Diuretics

Repeated studies have demonstrated that the prevalence of hypertension in any particular culture is directly related to the dietary sodium intake of those populations (90). Moreover, in cultures in which <60 mEq of sodium is consumed daily, arterial pressure does not increase with aging and hypertension is virtually nonexistent. In contrast, hypertension is highly prevalent in those industrialized societies in which sodium intake is higher (90,91). Diuretics seem to offset these effects by their natriuretic action and diuretics, when employed as single agents for the management of hypertension, have been effective for over 30 years (92).

Several mechanisms have been proposed for their antihypertensive action including 1) intravascular volume contraction; 2) reduced vascular responsiveness to naturally occurring vasoconstrictor substances and enhanced responsiveness to depressor substances; 3) decreased sodium content of the arterial wall; 4) altered transmembrane ionic exchange; 5) diminished baroreceptor activity; 6) induction of local tissue dilators (e.g., kinins, prostacylins) in the arterial wall; and 7) a direct vasodilating action on the arteriole (92,93).

Hemodynamic effects. The initial hemodynamic effect of diuretics relates to a decreased cardiac output in response to intravascular volume contraction produced by diuresis (92). However, within several weeks plasma volume and cardiac output return toward pretreatment levels and total peripheral resistance decreases. Thus, the net long-term hemodynamic effect of diuretic therapy is reduced total peripheral resistance, with minimal decreases in plasma and extracellular fluid volumes. Diuretics also induce a sustained rise in plasma renin activity and when therapy is stopped (even after several years), plasma volume expands and plasma renin activity decreases (92,93). This effect has been employed in treating patients with low renin essential hypertension in order to optimize conditions for angiotensin-converting enzyme inhibitors (94).

Clinical trials. Most of the major clinical trials have employed diuretics for initial monotherapy of essential hypertension, and, more recently, the Systolic Hypertension in the Elderly Program has used them for the treatment of isolated systolic hypertension (95). Moreover, the European Working Party Trial for Hypertension in the Elderly (80) and the Medical Research Council trial (77) have reaffirmed the safety and efficacy of these agents for the treatment of diastolic hypertension in elderly patients. Thus, the diuretics continue to be recommended as one of four major classes of therapeutic agents for first-line antihypertensive therapy (96).

Side effects. Diuretics have important metabolic side effects that may limit their use in other clinical conditions (e.g., hypokalemia, diabetes mellitus, hyperlipidemia, renal diseases, gout) (11,81). Hypokalemia has been implicated in the MRFIT study (81) as a possible factor in the sudden death of patients with cardiac involvement. As a result, the Joint National Committee (96) recommended reduced dosages of diuretics for pressure control because they are equally effective and induce less disturbing hypokalemia. Moreover, sodium restriction in patients treated with diuretics will diminish potassium wastage abetted by the induced hyperaldosteronism. Therefore, it seems reasonable to administer lower doses of the thiazide diuretics (e.g., 12.5 to 25 mg hydrochlorothiazide) and, if necessary, to prescribe a potassium-sparing agent (spironolactone, triamterene or amiloride) to protect patients with left ventricular hypertrophy, cardiac failure, digitalis therapy or chronic diarrhea from further ventricular irritability resulting from hypokalemia (96).

Angiotensin-Converting Enzyme Inhibitors

Mechanism of action. The first angiotensin-converting enzyme inhibitor was developed in the 1970s and introduced in the early 1980s for the treatment of hypertension (Table 1). These agents have emerged over the past 10 years as a major therapeutic option for the initial treatment of hypertension (97–100). They inhibit the conversion of angiotensin I to angiotensin II; they also inactivate circulating bradykinin, a potent naturally occurring vasodilating agent. Furthermore, they interfere with the interaction of angiotensin II with norepinephrine and with local tissue prostacyclin. They also reduce the formation of the heptapeptide, angiotensin III, which ultimately stimulates the adrenal cortical synthesis of aldosterone, thus decreasing a known sodium-retaining hormone (97). Hemodynamically, these agents lower arterial pressure by reducing total peripheral resistance without increasing heart rate, cardiac output or myocardial contractility. Renal blood flow may increase without altering glo-

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merular filtration rate, thereby reducing the glomerular filtration rate (100,101).

Clinical effects. In a multicenter study (101), captopril (50 to 75 mg daily) controlled arterial pressure in patients with mild to moderate hypertension and was as effective as hydrochlorothiazide (50 mg/day) (99,101,102). Captopril, enalapril and lisinopril are equally effective in reducing arterial pressure in patients with hypertension, and they have a low side effect profile. Nevertheless, they should be used with extreme caution in patients with renal functional impairment and in patients receiving potassium supplements or potassium-sparing agents. These agents may lead to hyperkalemia by either exacerbating renal insufficiency or inhibiting aldosterone production (103,104). They should not be administered to patients with bilateral renal artery disease or with arterial disease of solitary kidneys because renal failure and malignant hypertension may be produced (105–107).

Angiotensin-coverting enzyme inhibitors are particularly effective in hypertensive patients with high plasma renin activity states including congestive heart failure. These agents are also effective in patients with normal or low plasma renin activity and in anephric individuals, presumably because of the pressure of the renin-angiotensin system in vascular smooth muscle, myocardial and other extrarenal cells (97). Because of their beneficial renal hemodynamic effects, they are useful in patients with diabetes mellitus and with collagen vascular diseases (101,103).

Calcium Channel Antagonists

These agents represent another new class of antihypertensive compounds. Verapamil was the first to be synthesized (in the late 1950s), but was not made available for treatment of hypertension in the United States for almost 30 years. At present, a large number of such compounds have been released for treatment of hypertension and heart disease including nifedipine, diltiazem, nicardipine, isradipine, nitrendipine and others (96). Although all these agents are classed as calcium channel antagonists, they differ greatly with respect to chemical structure, physiologic action, and cardiovascular and renal hemodynamic problems.

Mechanism of action. Vasoconstriction, myocardial contractility and cardiac automaticity all depend on transmembrane calcium fluxes, and in these cells altered permeability of the calcium ion results in changes in vessel caliber and cardiac function (108–111). Therefore, calcium channel antagonists reduce intracellular influx of calcium, which results in reduced binding to the calmodulin, thus reducing contraction.

The calcium antagonists all produce arteriolar dilation and reduce arterial pressure with variable effects on cardiac output and myocardial contractility. Verapamil alters heart rate conduction, whereas nifedipine reflexively increases heart rate. Diltiazem has little effect on heart rate and depresses myocardial contractibility less than verapamil.

Clinical effects. In general, most studies have revealed that the calcium antagonists are as effective as the other classes of agents for reducing arterial pressure. They do so while maintaining an unchanged cardiac output and renal blood flow, as total peripheral and organ vascular resistances decrease (112–114). However, diltiazem increases renal blood flow while maintaining glomerular filtration rate by dilating efferent glomerular arteriolar resistance and, therefore, glomerular hydrostatic pressure (115).

The side effects of the calcium antagonists are minimal. The most frequent side effect of verapamil is constipation; diltiazem and nifedipine produce edema, and nifedipine also produces headache, flushing and dizziness (112,113).

Direct-Acting Vasodilators

Hydralazine. This drug was one of the first antihypertensive agents to produce arteriolar dilation and decreased total peripheral resistance through direct action on arteriolar smooth muscle (116,117). Many studies (118,119) have attested to the efficacy of hydralazine in lowering arterial pressure, but its principal clinical usefulness has been as an adjunct with other therapies rather than as a single agent (120,121). In the Veterans Administration cooperative study (22), hydralazine produced an additional decrease in mean arterial pressure of 7 mm Hg after the addition of hydrochlorothiazide. Several other studies (122,123), including another Veterans Administration study, showed that the thiazide-hydralazine combination produced a mean decrease of an additional 11 mm Hg in patients with mild to moderate hypertension.

The usefulness of hydralazine is limited by several side effects, which include reflex sympathetic stimulation and tachycardia (124). This increase in heart rate that generally accompanies hydralazine has been associated with precipitation of myocardial infarction in high risk patients (123). It does not affect plasma lipids or glucose adversely. However, it may increase antinuclear antibody titer consistent with a diagnosis of lupus erythematosus, hepatitis and peripheral neuropathy (123,125,126) in a dose-related fashion.

Minoxidil. This agent was initially synthesized in 1965; however, it was not approved for use as an antihypertensive agent until 1980 (Table 1). It is a potent vasodilator that acts as a direct arteriolar smooth muscle agent, thus reducing total peripheral resistance without modifying the sympathetic nervous system responses or increasing venous capacitance (127). Early studies (127,128) demonstrated its effectiveness in combination with propranolol in patients with refractory hypertension, and it has been particularly useful in severely hypertensive patients with chronic renal failure receiving hemodialysis. The limitations of minoxidil are marked sodium and water retention, edema, pulmonary hypertension and hirsutism (129,130). Pericardial effusions, angina pectoris and lupus reactions have been associated

with minoxidil (11,130,131). Therefore, minoxidil should not be used as a single agent, and it should be reserved for patients with refractory hypertension who have failed triple drug therapy.

Miscellaneous New Compounds

Several new and unique compounds have been synthesized to examine the pathophysiologic alterations in hypertension and include agents that antagonize serotonin, the statine substituted peptides that inhibit renin, and selective dopamine$_1$-receptor antagonists (132–137).

Ketanserin is a selective (S_2) serotonergic antagonist with additional alpha$_1$ adrenoreceptor blocking properties. The interaction between the two receptors seems to be necessary for its antihypertensive action (132,133). After the intravenous administration of ketanserin, arterial pressure decreases with minimal associated cardiovascular reflexive changes, and several studies (132,133) have shown greater efficacy in elderly, rather than younger, patients. Its major side effects include dizziness, somnolence and dry mouth, similar to those commonly observed with the centrally acting alpha$_2$-agonists.

The renin inhibitors are peptides with an unusual amino acid, statine, in their structures. These agents inhibit human renin and seem promising for the management of hypertension and as a physiologic probe. Although most studies have been performed in primates and animals with experimental hypertension (134,135), these agents have also been given to humans. Oral administration to conscious sodium-depleted marmosets resulted in significant blood pressure reduction secondary to complete inhibition of plasma renin activity.

Dopamine infusion increases arterial pressure, but infusion of a selective dopamine$_1$ agonist (fenoldopam) reduces arterial pressure while increasing renal blood flow and sodium excretion (136,137). Studies in humans have documented that by selective dopamine$_1$-receptor stimulation, arterial pressure is decreased through a reduction in total peripheral resistance with associated reflex cardiovascular stimulation (136,137).

A Perspective on the Treatment of Arterial Hypertension

The Veterans Administration cooperative studies (96) over the past 30 years have clearly demonstrated a reduced morbidity and mortality with adequate control of arterial pressure. These initial multicenter studies were followed by numerous large scale clinical trials (138,139) involving >50,000 patients, all of which confirmed the initial observation. In the earlier studies, a diuretic agent was prescribed initially and, if necessary, an antiadrenergic agent (e.g., reserpine, methyldopa, beta-blocker) was added, followed by a direct-acting smooth muscle vasodilator (i.e., hydralazine). This stepped-care approach was not only physiologically rational, but also empirically sound. The diuretic was added first to prevent pseudotolerance of the expansion of intravascular volume with the second and third step agents (36,37). More recently other classes of antihypertensive agents were introduced and found to be as efficacious as "first step" therapy. These include the beta-adrenoreceptor inhibitors, calcium antagonists and the angiotensin-converting enzyme inhibitors (36,37,63,66,101,112–114). Thus, all four classes of compounds reduce pressure without intravascular volume expansion. Moreover, continued use of these agents has provided considerable insight into their efficacy, with concomitant diseases frequently encountered in patients with hypertension. With this additional information, it has now become possible to tailor a therapeutic regimen for individual patients, especially those with multiple diseases in whom one agent may serve the purpose of treating more than one disease.

Coronary Artery Disease

Ischemic heart disease is usually associated with arterial spasm or atherosclerotic occlusive disease of the coronary arteries. Patients with hypertension and coronary artery disease have increased myocardial tension and myocardial oxygen demands on the basis of the elevated pressure and increased cardiac size; these may be aggravated by the restricted blood flow offered by coronary artery disease (86). Thus, an ideal therapeutic agent in these patients would be one that improves coronary circulation, decreases pressure overload imposed on the left ventricle and reduces myocardial oxygen demand.

Beta-adrenergic blockers. Coronary artery disease is a major cause of death in the United States, and hypertension is among its leading treatable risk factors (140). Many studies investigating the interrelation between hypertension and other risk factors associated with the development of coronary artery disease utilized a variety of antihypertensive agents to demonstrate that reduction of arterial pressure reduced overall morbidity and mortality (20–23,77–84, 138,139). Beta-adrenoreceptor blocking agents were used in many of these studies (78–84). They have the advantage of reducing the "double product," (i.e., the product of systolic pressure and heart rate), which is a major determinant of myocardial tension. Thus, these agents reduce myocardial oxygen demand and improve myocardial performance (25). The beta-adrenoreceptor blockers, because of their peripheral vasoconstrictive effects, should be used with caution in patients with diffuse peripheral vascular disease. However, nadolol and atenolol have been shown to improve the renal circulation in patients with hypertension (63,64).

Most beta-adrenoreceptor blockers adversely affect lipid profiles (e.g., decrease the HDL/LDL lipoprotein ratio). However, this ratio is not affected by beta-adrenoreceptor

antagonists with intrinsic sympathomimetic activity (75,76). These agents primarily increase the low density lipoprotein component in the blood, whereas others may have effects on triglyceride (76).

Diuretics. Most large scale clinical trials (78–84) have also utilized diuretics alone or in combination with other agents for control of arterial hypertension in patients with coronary artery disease. Because these agents may produce various electrolyte and metabolic side effects (e.g., hypokalemia, hyperglycemia, increased cholesterol levels and hyperuricemia) (10,11), it is possible that they might have attenuated their overall effectiveness in preventing myocardial infarction and sudden death (81,141). Hypokalemia associated with an abnormal electrocardiogram or with left ventricular hypertrophy may increase mortality of patients with coronary heart disease independent of its effect on blood pressure (81,142). Thus, patients using diuretics should have their serum potassium levels followed carefully (and corrected, if necessary) to prevent these problems. Moreover, if single-agent therapy is desired and hypercholesterolemia is of concern, it might be prudent to use an alternative single agent (e.g., a calcium antagonist or an angiotensin-converting enzyme inhibitor). These latter agents usually do not cause significant alterations in serum potassium, glucose, uric acid or lipids, each of which contributes to risk of coronary disease (98,143).

Angiotensin-converting enzyme inhibitors and calcium channel blockers. The angiotensin-converting enzyme inhibitors reduce total peripheral resistance without increasing heart rate and, therefore, serve to reduce myocardial and oxygen demand while maintaining renal blood flow (107, 144). The calcium antagonists also attenuate the peripheral vasoconstrictor response to catecholamines and alter calcium influx into vascular smooth muscle, thereby reducing coronary artery spasm and myocardial oxygen demand while improving coronary blood flow (109–111,145). Furthermore, calcium antagonists have been shown in experimental studies (146) to reduce atherogenesis, a major factor in the pathogenesis of coronary artery disease. Therefore, the optimal agents for treatment of hypertension in patients with coronary artery disease would be those groups of drugs that control arterial pressure without adversely affecting electrolytes, plasma lipids or other metabolic processes, thereby improving myocardial oxygen demand and left ventricular afterload. Therefore, the calcium channel antagonists, angiotensin-converting enzyme inhibitors and some of the beta-adrenoreceptor blockers would be optimal for such patients.

Myocardial Infarction

Role of antihypertensive agents. Hypertension has a profound, deleterious effect on the clinical course of patients with acute myocardial infarction or unstable angina pectoris (147). The elevated arterial pressure that results in increased ventricular afterload and outflow tract impedance also increases myocardial oxygen demand, further limiting ventricular function (86). Many studies (148,149,151) have shown that reduction of pressure, especially with agents that reduce myocardial oxygen consumption, preserve or improve myocardial function and reserve. Such agents reduce mortality after a myocardial infarction; they include the beta-adrenoreceptor blockers without intrinsic sympathomimetic activity and the calcium antagonist diltiazem in the patients with non-Q wave infarction (150,151). However, none of the calcium antagonists and only the beta-adrenoreceptor antagonist timolol has been shown to limit infarct size or prevent myocardial infarction (148,152). Likewise, the angiotensin-converting enzyme inhibitors have not prevented reinfarction of myocardium, although captopril, in preliminary trials (152–157) has been shown to protect the heart from developing subsequent cardiac failure after myocardial infarction. This action of captopril in the postinfarction period has been attributed to the concept of "remodeling" of the myocardium; however, the mechanism is unclear. As a group, angiotensin-converting enzyme inhibitors are beneficial in these patients because they reduce total peripheral resistance and myocardial oxygen demand without increasing heart rate in the postmyocardial infarction period (153).

Clearly, arterial pressure control by venodilation with nitrates and other antihypertensive agents relieves symptoms of coronary ischemia. However, in contrast to the aforementioned drugs, agents such as nitroprusside and nitroglycerin, while reducing pressure and improving coronary blood flow, also increase heart rate and myocardial oxygen demand (148). Thus, drugs that reduce myocardial oxygen demand, improve pump function and diminish end-diastolic volume and myocardial tension are preferred in this clinical setting.

Risk of excessive blood pressure reduction. Finally, recent reports have suggested that patients with hypertension who are treated vigorously with antihypertensive agents and whose diastolic arterial pressures are reduced to levels <90 mm Hg may demonstrate a greater predisposition to myocardial infarction and increased death rate (84,158). This so-called J-shaped curve of cardiovascular morbidity and mortality has been explained variously by excessive reduction of pressure and too-vigorous use of antihypertensive agents (159,160). An additional possibility is that these patients with greater pressure reduction initially had more severe hypertension and vascular disease and required the greater decrement of diastolic pressure. Clearly, this is an area of current controversy that demands clarification.

Congestive Heart Failure

Hypertension-induced heart failure. Approximately one-half million people develop congestive heart failure each year in the United States; hypertension is the major caus-

ative factor (161). In those patients with hypertension-induced left ventricular failure, the primary goal of therapy is to control pressure and ultimately reduce left ventricular pressure overload. Treatment involves the use of agents that diminish left ventricular preload and afterload as well as those that reestablish normal electrolyte balance by attenuating the effects of the secondary hyperaldosteronism (154–157). The angiotensin-converting enzyme inhibitors alone, or in conjunction with diuretics or digitalis, are particularly useful in this setting.

Hormonal factors. Elevated plasma catecholamine levels have correlated with mortality in patients with congestive heart failure (162). However, other humoral pressor substances, such as vasopressin and angiotensin II, are also elevated in cardiac failure (163). Pharmacologic agents that modify these hormonal actions would also improve myocardial function.

Preferred therapeutic agents. Several studies have evaluated the role of calcium antagonists, angiotensin-converting enzyme inhibitors, beta-adrenoreceptor blockers, diuretics and vasodilators in improving ventricular function in patients with congestive heart failure with or without hypertension (147,150,154,164,165). These studies have shown that these agents reduce mortality by ≥50% in patients with New York Heart Association class I and II congestive heart failure. In addition, the angiotensin-converting enzyme inhibitors were shown to have a beneficial effect in patients with New York Heart Association class IV congestive heart failure (154,155). However, these studies also demonstrated that the beta-adrenoreceptor blockers and calcium antagonists are relatively contraindicated in patients with severe cardiac failure.

Diuretic therapy in cardiac failure is fraught with the intrinsic danger of electrolyte and acid-base problems (specifically, hypokalemia, hypomagnesemia and alkalosis) (81,140). The angiotensin-converting enzyme inhibitors will help circumvent this problem by permitting the use of lower doses of diuretics (94). Recent studies (166) have suggested that the shorter-acting angiotensin-converting enzyme inhibitors might have an advantage over the longer-acting agents, possibly because of their effects on renal function in patients with heart failure. Thus, in patients with congestive heart failure, the angiotensin-converting enzyme inhibitors, and perhaps cautiously administered calcium channel blockers, are indicated for the control of arterial pressure. These agents would serve to complement the therapeutic armamentarium of diuretics, digitalis and nitrates.

Mitral Valve Prolapse

This problem has been related to a variety of causes ranging from myxomatous degeneration of the mitral valve leaflets to the functional creation of prolapse by enhanced myocardial contractility on the posterior valve leaflet (167). Hemodynamically, these effects may result in mitral regurgitation, cardiac arrhythmias and chest discomfort. When hypertension is present, left ventricular hypertrophy may also occur.

Agents that have been beneficial to relieve the symptoms associated with mitral valve prolapse, the altered function, as well as the elevated arterial pressure, include the beta-adrenoreceptor blocking agents or calcium antagonists (167).

Hyperkinetic Heart Syndrome

Many patients with hypertension, particularly young patients with milder degree of severity of the disease, have a hyperdynamic circulation that is manifested by a higher cardiac output, faster heart rate, increased myocardial contractility and oxygen consumption and, in some, increased responsiveness to circulating catecholamines (168,169). The mechanism for the increase in cardiac output has been shown to be increased adrenergic function or enhanced beta-adrenoreceptor responsiveness. Clinically, these patients complain of palpitation, extra heartbeats and tachycardia; sometimes their symptoms are reproducible or aggravated by isoproterenol infusion (170). The beta-adrenoreceptor blocking agents appear to provide the best treatment for these patients. However, if they are contraindicated because of other preexisting medical conditions, other adrenergic inhibitors or the calcium antagonists may serve as an alternative therapy.

Left Ventricular Hypertrophy

Several studies (171–173) have shown that left ventricular hypertrophy, as assessed by echocardiography, is common in patients with hypertension. This hypertrophy is an independent risk factor for cardiovascular morbidity and mortality (142,172,173). Because the increased geometry of left ventricle is a major determinant of ventricular tension, this factor (and the increased intraventricular systolic pressure) may explain some of this risk (86). Left ventricular hypertrophy impairs coronary artery blood flow, which leads to a relative coronary ischemia in the presence of atherosclerotic occlusive coronary disease, a process further exacerbated by hypertension (85,86). Thus, control of arterial pressure will reduce myocardial oxygen consumption and help potentiate regression of left ventricular hypertrophy (24,25).

Agents to reduce left ventricular mass. Most agents that reduce arterial pressure and maintain that reduction for a long period of time will decrease left ventricular mass, although minoxidil may actually increase left ventricular mass despite regulation of arterial pressure (174). Of the agents that diminish left ventricular mass, some have been shown experimentally and clinically to work faster than others (175,176). Thus, within 3 weeks experimentally, and from 4 to 12 weeks clinically, the centrally active adrenergic

inhibitors, the angiotensin-converting enzyme inhibitors and calcium antagonists reduce left ventricular mass (25–29).

The mechanisms by which these drugs seem to diminish left ventricular mass is unknown; however, they seem to involve nonhemodynamic, as well as hemodynamic, factors (176). Methyldopa is the protype of the centrally acting agents (27–29). Clonidine does not reduce mass unless the dose providing hemodynamic effects equivalent to those of methyldopa is tripled; then it acts as a peripheral alpha-adrenergic receptor agonist to increase pressure and total peripheral resistance (28). In addition to this intriguing hemodynamic/nonhemodynamic dissociation is the finding that methyldopa reduces the mass of the nonhypertrophied left ventricle of normontensive rats, as well as of the nonhypertrophied right ventricle (28,177). The angiotensin-converting enzyme inhibitors and calcium antagonists also reduced left ventricular mass in experimental as well as clinical hypertension (97,111–114,175,176,178,179). They do not decrease right ventricular mass, although some angiotensin-converting enzyme inhibitors may also diminish the mass of the nonhypertrophied normotensive rat left ventricle (178).

Clinical effects. Clinical studies have yet to demonstrate the record of risk from regression of left ventricular hypertrophy, although a preliminary report from the Framingham Heart Study (180) supplies some data. Still to be demonstrated is the lessening of risk with reversal of ventricular hypertrophy independent of arterial pressure control. Moreover, there are no clinical studies showing improved function of the left ventricle with pharmacologically reduced mass. Methyldopa (177) and captopril (181), in fact, induced no improvement or even caused deterioration of left ventricular pumping ability at normal or elevated arterial pressures. Clearly, this is an active area of study and new and exciting information will undoubtedly be forthcoming in the near future.

Peripheral Vascular Disease

Role of antihypertensive agents. The most common diseases of the aorta and peripheral vessels are aneurysms and occlusive arterial disease (182). They are more frequently seen in patients with diabetes mellitus, hyperlipidemia or hypertension, or combinations (182,183). Cigarette smoking significantly increases the probability of occlusive arterial disease in such patients (183). Although it would seem that agents that control elevated arterial pressure should improve peripheral vascular disease, until recently this had not been demonstrated. Agents such as calcium antagonists, angiotensin-converting enzyme inhibitors, and alpha$_1$-adrenoreceptor blockers, which do not exacerbate symptoms of peripheral arterial insufficiency, have been useful in controlling arterial pressure in these patients. Conversely, beta-adrenoreceptor blockers would be expected to exacerbate symptoms of claudication by their peripheral vasoconstricting effect (66).

Dissecting aortic aneurysm. Antihypertensive drugs that should be selected to manage patients with dissecting aortic aneurysm should decrease arterial pressure without reflexively increasing the shearing forces on the aortic wall (11,15). From among these, the ganglionic blocker trimethaphan, the alpha-/beta-adrenoreceptor blocking agent labetalol possibly the angiotensin-converting enzyme inhibitor, enalaprilat and sodium nitroprusside are those that satisfy these criteria. The vasodilators hydralazine and diazoxide are contraindicated unless there is preexisting protection with a beta-adrenoreceptor blocking drug (11,15).

Conclusions. Because of these recent advances in our understanding of the pathophysiology and pharmacology of hypertension, management of this disease should no longer be considered as empiric. The clinician now has the opportunity to prescribe therapy that not only will control arterial pressure and provide benefit to the heart, kidneys and other organs, but also can be selected so that it will not exacerbate concomitant diseases (e.g., gout, diabetes, hyperlipidemia) or create new problems. Moreover, with continuing advances and with new focus on the molecular mechanisms of disease and in designing new therapy (e.g., renin inhibitors), enlightened insights into the pathophysiology of the disease and more specific therapy will no doubt ensue. These past 4 decades have been exciting and satisfying; those ahead will no doubt be astounding.

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